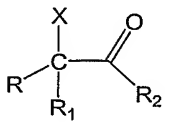
CATALYTIC ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE α-HALO-CARBONYL COMPOUNDS

Background

The present invention is related to a process for the catalytic asymmetric synthesis of optically active α-halo-carbonyl compounds of the formula (1)



(1)

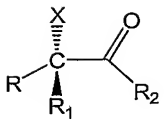
wherein R is an organic group; X is halogen; R_1 and R_2 which may be the same or different represents H, or an organic group, or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2 when different from H is attached through a carbon-carbon bond.

An important goal for asymmetric catalysis is to develop new reactions affording optically active building blocks using simple and easily-available starting materials and catalysts. Optically active halogen containing compounds are especially attractive due to their high value as synthetic intermediates. Despite intensive research efforts over the past years, examples of highly enantioselective halogenation reactions are scarce and often limited to 1,3-dicarbonyl compounds or multi-step procedures requiring expensive reagents.

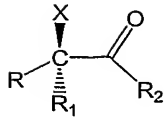
The compounds of general formula (1) are *e.g.* useful intermediates for the syntheses of pharmaceuticals such as antibiotics, agrochemicals, raw materials for chemicals and the like.

Description of the invention

In a first embodiment, the present invention provides a one-step catalytic asymmetric process for the synthesis of an optically active compound of formula (1a) or (1b)



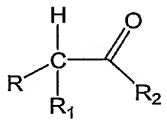
(1a)



(1b)

wherein R is an organic group; X is halogen; R_1 and R_2 which may be the same or different represents H or an organic group, or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2 when different from H is attached through a carbon-carbon bond and,

comprising the step of reacting a compound of the formula (2)



(2)

with a halogenating agent and in the presence of a catalytic amount of a chiral nitrogen containing organic compound.

The compound represented by the general formula (1) is not limited to specified ones, as long as the object of the present invention is not hindered. In the general formula (1), R, R_1, R_2 includes, for instance, alkyl groups, alkenyl groups, alkynyl groups, haloalkyl groups, alkylaryl groups, aryl groups and heterocyclic groups, each of which may have one or more substituents.

For convenience, certain terms employed in the specification, examples and claims are collected here.

The term "catalytic amount" is recognized in the art and means a sub-stoichiometric amount relative to a reactant. As used herein, a catalytic amount means from 0.0001 to 90 mole percent relative to a reactant, preferably from 0.001 to 50 mole percent, and more preferably from 0.1 to 20 mole percent relative to a reactant.

The term "enantiomeric excess" (ee) is well known in the art and is defined for a resolution of the racemic mixture

ab → a + b as

$$ee_a = \left(\frac{\text{conc. of a - conc. of b}}{\text{conc. of a + conc. of b}} \right) \times 100$$

The value of ee will be a number between 0 and 100, zero being racemic and 100 being pure single enantiomer.

The term "alkyl" refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Moreover, the term alkyl as used throughout the specification and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a hydroxyl, a carbonyl, an alkoxyl, an ester, a phosphoryl, an amine, an amide, an imine, a silyl, a silyl ether, a thiol, a thioether, a thioester, a sulfoxide, a sulfonyl, an amino, a nitro, a phosphino, a phosphate, an aryl, a heterocycle or an organometallic moiety. Representative examples of the alkyl group include groups having 1 to 20 carbon atoms in its hydrocarbon backbone, preferably 1 to 10 carbon atoms. When appropriate the number of carbon atoms designated in the hydrocarbon backbone for a substituent is assigned (i.e. C_{1-7} means one to seven carbons). It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term "alkenyl" refers to linear or branched groups of 2 to about 20 carbon atoms or, preferably, 2 to about 8 carbon atoms, having at least one carbon-carbon double bond. The term is intended to include both "unsubstituted alkenyls" and "substituted alkenyls" as described for alkyl above.

The term "alkynyl" refers to linear or branched groups of 2 to about 20 carbon atoms or, preferably, 2 to about 8 carbon atoms, having at least one carbon-carbon triple bond. The term

is intended to include both "unsubstituted alkynyls" and "substituted alkynyls" as described for alkyl above.

The term "haloalkyl" refers to an alkyl group, as defined above, wherein one or more hydrogen atoms are replaced by a halogen atom.

The term "aryl" refers to a carbocyclic aromatic system containing one or more rings wherein such rings may be attached together in a pendent manner or may be fused. Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogens, alkyls, haloalkyls, alkenyls, alkynyls, hydroxyl, amino, nitro, thiol, amines, imines, amides, carbonyls, carboxyls, ethers, thioethers, sulfonyls, sulfoxides, phosphinos, phosphonates, ketones, aldehydes, esters or the like.

The term "alkylaryl" refers to aryl-substituted alkyl groups. Preferable alkylaryl groups are "lower alkylaryl" groups having aryl groups attached to alkyl groups having 1 to 6 carbon atoms. Even more preferred lower alkylaryl groups are phenyl attached to alkyl portions having 1 to 3 carbon atoms. Examples of such groups include benzyl, diphenylmethyl and phenylethyl. The aryl in said alkylaryl may be additionally substituted as defined above. When appropriate the number of carbon atoms designated in the hydrocarbon backbone of the alkyl part is assigned (i.e. C_{1-3} alkylaryl means an alkylaryl group where the alkyl part contains one to three carbon atoms).

The term "heterocyclic" refers to 3 to 10-membered ring structures, which include at least one heteroatom preferably selected from O, S or N, and which may be aromatic (heteroaryl). Examples of such structures include pyridine, pyrimidine, piperidine, triazole, thiophene, furane, morpholine, chromane, indole, oxazole etc. The heterocycle may be substituted in one or more ring positions as mentioned for the aryl groups.

The term "amino" refers to a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or phenyl substituent and the tertiary amino group carrying two similar or different substituents or the two nitrogen

substituents together forming a ring. The substituents may be additionally substituted as defined above, and as such the amino group may form part of an amino acid moiety.

The term "silyl" refers to the $-SiZ_1Z_2Z_3$ group, where each of Z_1, Z_2 and Z_3 is independently selected from the group consisting of hydrogen and optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocyclic, alkoxy and amino.

The term "phosphino" refers to the group $-PZ_1Z_2$, where each of Z_1 and Z_2 is independently selected from the group consisting of hydrogen and optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocyclic and amino.

The term "phosphate" refers to the group $-O(P=O)(OZ_1)(OZ_2)$ where Z_1 and Z_2 is independently selected from the group consisting of hydrogen and optionally substituted alkyl and aryl,

The term "thio" is used herein to refer to the group $-SZ_1$, where Z_1 is selected from the group consisting of hydrogen and optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl and heterocyclic.

The term "sulfoxide" refers to the group $-S(=O)Z_1$ where Z_1 is selected from the group consisting of optionally substituted alkyl and alkylaryl.

The term "sulfonyl" refers to the group $-SO_2Z_1$ where Z_1 is selected from the group consisting of optionally substituted alkyl and alkylaryl.

When two substituents are bridged together, they are joined through a bridging group, *e.g.* via an alkylene, alkenylene, or alkynylene radical chain optionally with one or more of the carbon atoms substituted with a heteroatom, said chain optionally being substituted with one or more substituents.

The term "halogen" designates F, Cl, Br or I.

When any variable may occur more than one time in any formula for a compound, its definition on each occurrence is independent of its definition at every other occurrence.

R is preferably an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{2-8} alkylene group or a C_{1-3}-alkylaryl group. More preferably R is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-4} alkylene group or a C_{1-2}-alkylaryl group.

R_1 is preferably H or an optionally substituted C_{1-10} alkyl group.

R_2 is preferably H or an optionally substituted C_{1-10} alkyl group or R and R_2 are bridged together forming part of a ring system. More preferably R_2 is H or together with R forms an optionally substituted C_{3-5}-alkylene bridge.

X is preferably F, Cl or Br.

In a preferred embodiment of the present invention R_1 and R_2 both represents H and R represents an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{2-4} alkylene group or a C_{1-2}-alkylaryl group. More preferably R is attached through a $-CH_2-$ group.

In another preferred embodiment of the present invention R_1 is H and R and R_2 each represents an optionally substituted C_{1-10} alkyl group or R_2 together with R forms an optionally substituted C_{3-5}-alkylene bridge optionally with one or more of the carbon atoms being replaced by a heteroatom.

In principle any solvent that is capable of dissolving the reagents and the catalysts in suitable amounts and which is inert with respect of the reaction may be used. The solvent employed in the reaction may be either protic, aprotic, mixtures of both or ionic liquids. Suitable protic solvents include, water, alcohols *e.g.* straight, branched or cyclic alkanols and halogenated alkanols, aromatic alcohols; amines and organic acids. Suitable aprotic solvents include dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), *N*-methylpyrrolidone, dimethylsulfoxide (DMSO), pyridine, alkanes and haloalkanes, ethers, ketones, aldehydes, nitriles, and nitroalkanes. The compound of formula (2) may also serve the purpose of solvent

when in its liquid state at the reaction temperature.

Examples of halogenating agents are: *N*-halogenated amides such as, *N*-halosuccinimides *e.g.* *N*-chlorosuccinimide, *N*-bromosuccinimide or *N*-iodosuccinimide, *N*-halophthalimide *e.g.* *N*-chlorophthalimide, *N,N'*-dihalodimethylhydantoin *e.g.* *N,N'*-dichlorodimethylhydantoin, *N*-halosaccharine *e.g.* *N*-chlorosaccharine or *N*-bromosaccharine, 1,3,5-trihalo-1,3,5-triazine-2,4,6-trione *e.g.* 1,3,5-trichloro-1,3,5-triazine-2,4,6-trione, *N*-haloglutarimide *e.g.* *N*-chloroglutarimide, *N*-chloro-N-cyclohexyl-benzenesulfonimide; interhalogen compounds such as ICl or IBr; SO_2X_2 *e.g.* SO_2Cl_2; $(Ph)_3PX_2$ *e.g.* $(Ph)_3PCl_2$ or $(Ph)_3PBr_2$; $(Ph)_3/CX_4$ *e.g.* $[(Ph)_3CCl_3]Cl$; complexed halogens such as pyridin-HBr-Br_2 or $(CH_3)_2S$-Br_2; t-BuOCl; elemental halogen *e.g.* Cl_2 or Br_2; 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one; 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one; 4,4-dibromo-2,6-di-tert-butyl-cyclohexa-2,5-dienone and electrophilic fluorinating agents such as *N*-fluorodibenzenesulfonimide (NFSI), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor®) and 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate).

Preferred halogenating agents are *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), 4,4-dibromo-2,6-di-tert-butyl-cyclohexa-2,5-dienone and *N*-fluorodibenzenesulfonimide (NFSI).

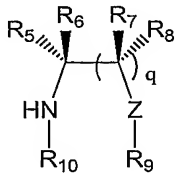
The amount of halogenating agent relative to the compound (2) depends on the amount of 'active' haloatoms on the halogenating agent, but in case of one active haloatom as in *N*-halosuccinimide, the amount is usually 0.25-4 equivalents, preferably 0.25-2.5.

It has further been found that addition of acids to the reaction media has a positive effect on the reaction rate and yield of the compound (1). Preferably the acid(s) is selected among carboxylic acids such as aliphatic and aromatic carboxylic acids. Examples of such acids are acetic acid, trifluoroacetic acid, chloroacetic acid, benzoic acid and nitro substituted benzoic acids *e.g.* 2-nitrobenzoic acid. The amount of acid relative to the compound (2) is 0-200 mole percent, preferably 0-60 mole percent.

Any chiral nitrogen containing organic compound capable of inducing asymmetric

halogenation can be used as catalyst. Preferred are catalysts having a primary or secondary nitrogen atom. It is to be understood that the chiral nitrogen containing organic compound may be used as such or when appropriate in one of its salt forms.

Examples of the chiral nitrogen containing organic compound used as catalyst include, but are not limited to, the following compound (3):



(3)

wherein q is 0 or 1;

R_5, R_6, R_7, R_8, which may be the same or different represents H, alkyl, haloalkyl, alkoxyl, OH, amino, amide, silyl, silyl ether, COR_{11}, optionally substituted aryl, an optionally substituted heterocycle, alkyl substituted with at least one OH group, an optionally substituted amino group or optionally substituted aryl or heterocycle or R_5 and R_6 together or R_7 and R_8 together may represent a carbonyl group or when q is 1, R_5 with either R_7 or R_8 may be bridged together forming part of a ring system;

R_{11} represents an optionally substituted amino group or OR_{12} wherein R_{12} represents H, alkyl or phenyl;

R_9 and R_{10}, which may the same or different represents H, alkyl, OH, alkoxy or

R_9 and R_{10} may be bridged together forming part of a ring system;

Z is S, O, C=O, $C(R_{14})_2$, N-R_{14} wherein R_{14} is R_5;

with the provisio that the groups R_5, R_6, R_7, R_8, R_9, R_{10}, R_{14}, and Z are selected so that the compound (3) is a chiral compound.

It is within the capabilities of the skilled person to select suitable groups R_5, R_6, R_7, R_8, R_9, R_{10}, R_{14}, and Z so that the compound (3) will be a chiral compound. It will be immediately apparent for the skilled person which limitation this provisio provides to the selection. For example if q is 0 then may R_5 and R_6 be selected so that R_5 is different from R_6 and if q is 1 the may R_5, R_6, R_7 and R_8 be selected so that at least one of R_5, R_6, R_7 and R_8 is different from the three other of these.

In a preferred embodiment of the present invention, q is 1; R_5, R_6, R_7, R_8 which may be the same or different represents H, COR_{11}, optionally substituted aryl preferably phenyl or benzyl, or methyl substituted with at least one of the following, an OH group, an optionally substituted amino group or an optionally substituted aryl or heterocycle group; or R_5 and R_7 together represents a C_{3-5} alkylene bridge;

R_{11} represents OH, NH_2 or NH-alkyl;

R_9 and R_{10} are H or R_9 and R_{10} together represents a methylene bridge optionally substituted with phenyl, benzyl, COOH or CO– alkoxy;

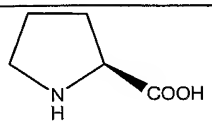
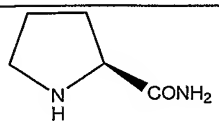
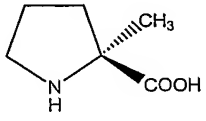
Z is CH-R_{14} or N-R_{14} wherein R_{14} represents H or alkyl.

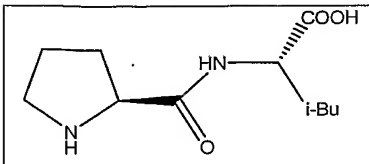
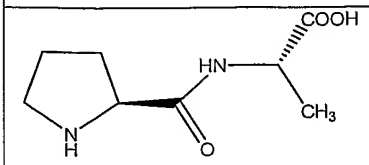
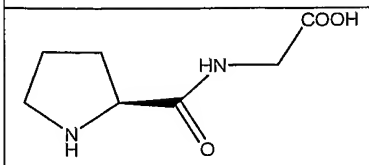
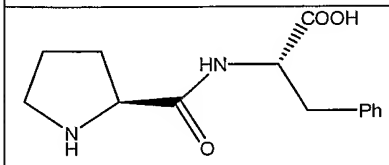
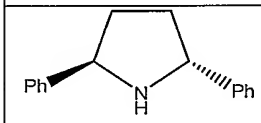
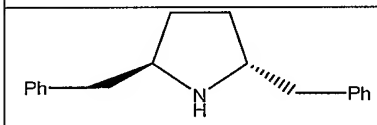
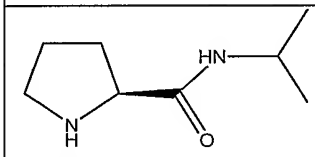
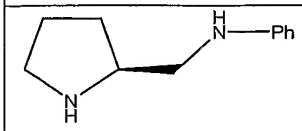
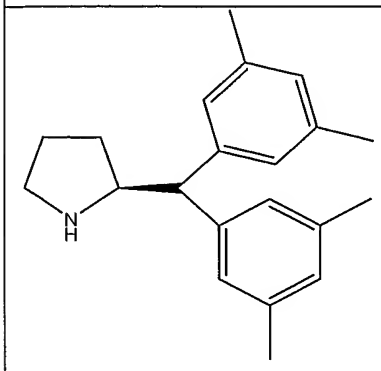
In a more preferred embodiment the substituent pair (R_5/R_6) is identical to the pair (R_7/R_8).

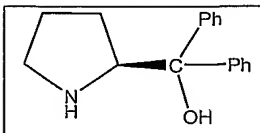
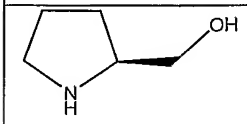
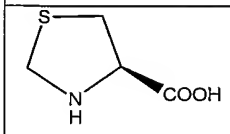
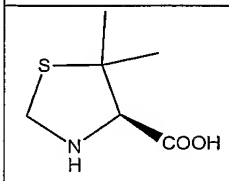
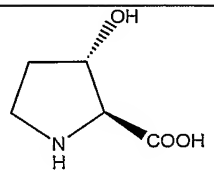
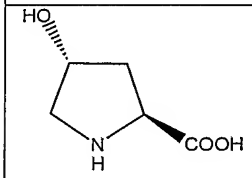
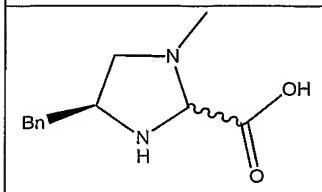
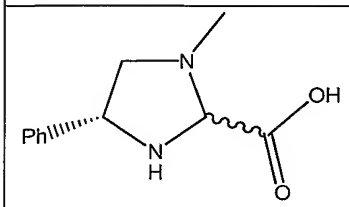
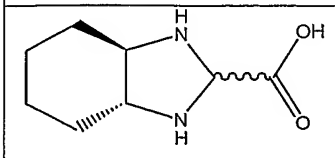
In an even more preferred embodiment either R_5 or R_6 represents H; R_7 and R_8 represents H; R_9 and R_{10} together represents a methylene bridge and Z is CH_2.

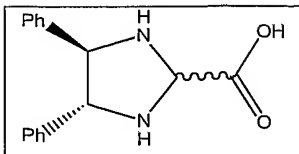
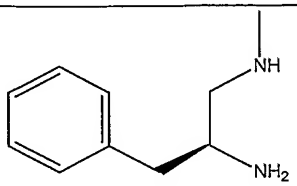
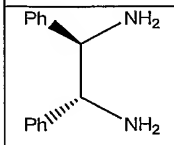
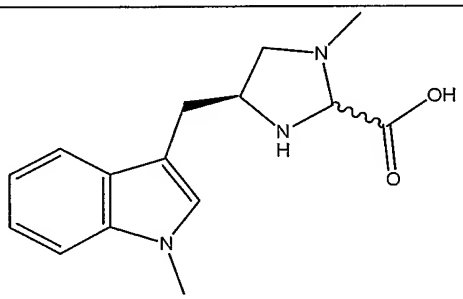
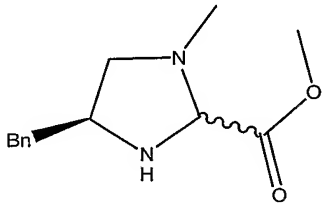
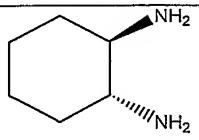
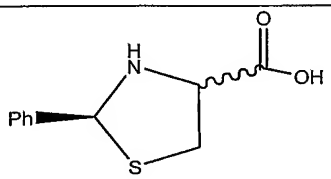
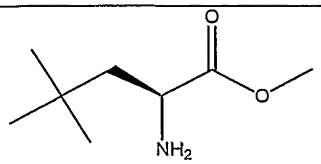
The chiral nitrogen containing organic compound used as catalyst may be chosen among the compounds shown in Table 1a, where the stereoconfiguration shown merely serves an illustrative purpose:

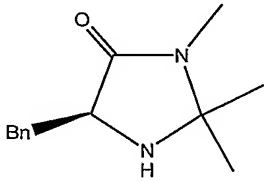
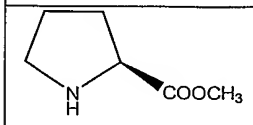
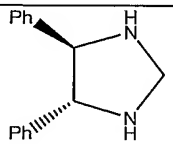
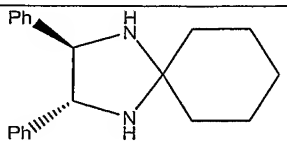
Table 1a

Structure	Name
	L-proline
	L-prolinamide
	2-methyl-L-proline

	L-prolyl-L-leucine
	L-prolyl-L-alanine
	L-prolylglycine
	L-prolyl-L-phenylalanine
	(2*R*,5*R*)-diphenylpyrrolidine
	(2*R*,5*R*)-dibenzylpyrrolidine
	*N*-(1-methylethyl)-(2*S*)-pyrrolidinecarboxamide
	(2*S*)-(anilinomethyl)pyrrolidine
	(2*S*)-[bis(3,5-dimethylphenyl)methyl]-pyrrolidine

	diphenyl((S)-pyrrolidin-2-yl)methanol
	L-prolinol
	(4*S*)-thiazolidinecarboxylic acid
	5,5-dimethyl-(4*S*)-thiazolidinecarboxylic acid
	*trans*-3-hydroxy-L-proline
	*trans*-4-hydroxy-L-proline
	(4*S*)-benzyl-1-methyl-imidazolidine-2-carboxylic acid
	1-methyl-(4*R*)-phenyl-imidazolidine-2-carboxylic acid
	(4*R*,5*R*)-octahydro-benzoimidazole-2-carboxylic acid

	(4*S*,5*S*)-diphenyl-imidazolidine-2-carboxylic acid
	(*S*)-N^1-methyl-3-phenyl-propane-1,2-diamine
	(1*R*,2*R*)-diphenylethanediamine
	1-methyl-(4*S*)-(1-methyl-1H-indol-3-ylmethyl)-imidazolidine-2-carboxylic acid
	(4*S*)-benzyl-1-methyl-imidazolidine-2-carboxylic acid methyl ester
	(1*R*,2*R*)-cyclohexanediamine
	(2*S*)-phenyl-thiazolidine-4-carboxylic acid
	(*S*)-*tert*-leucine methyl ester

	(5*S*)-benzyl-2,2,3-trimethyl-imidazolidin-4-one
	L-methyl prolinate
	(*R*,*R*)-4,5-diphenylimidazolidine
	(*R*,*R*)-2-cyclohexyl-4,5-diphenylimidazolidine

The selection of the stereochemistry of the catalyst depends on the stereochemistry of the desired compound and by proper choice of catalyst one can prepare compounds of either formula (1a) or (1b) as illustrated in the examples. The catalyst can be bound to a support or be unsupported.

The amount of catalyst may be as high as 90 mole percent relative to the compound (2). In principle there is no lower limit to the amount of catalyst employed, however, in practice the desire of a suitable high reaction rate dictates a certain lower limit. The catalyst may conveniently be separated from the final reaction mixture and reused in subsequent reactions according to the present invention.

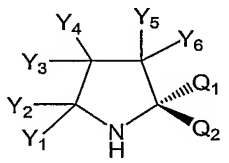
The reaction may conveniently be carried out at temperatures between –90 °C and 100 °C, preferably between -30 °C to 50 °C.

No displacement of any other substituents with halogen other than the α-hydrogen atom on the compound (2) is observed in the reaction according to the present invention.

The starting compound (2), and the chiral nitrogen containing organic compounds used as

catalysts are commercially available or can be synthesized according to known methods.

Within the general formula (3) are a subclass of novel catalysts of formula (4) which have been found to show a remarkable catalytic effect in asymmetric synthesis of optically active α-halo-carbonyl compounds, in particular α-fluoro-carbonyl compounds, even when applied in amounts less than 5 mol% relative to the compound (2):



(4)

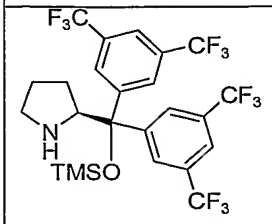
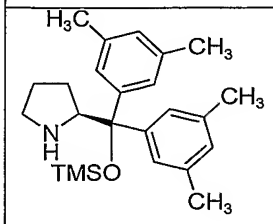
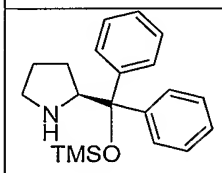
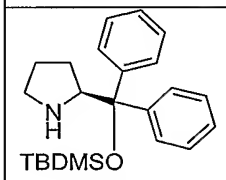
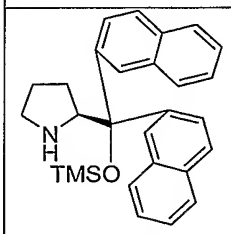
wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6 which may be the same or different represents H, an alkyl, haloalkyl, an aryl, an alkylaryl, a heterocycle, a halogen, a hydroxyl, a carbonyl, an alkoxyl, an ester, an amine, an amide, a silyl, a silyl ether, or Y_2 and Y_3 or Y_4 and Y_5 may be bridged together forming part of a ring system one of Q_1 and Q_2 represent H, alkyl, haloalkyl, alkylaryl and the other the group $CY_7Y_8(OY_9)$ wherein Y_7 and Y_8 which may be the same or different represents alkyl, haloalkyl, an alkylaryl, a heterocycle, or optionally substituted aryl and Y_9 represents a silyl group.

In a preferred embodiment of the present invention Y_1, Y_2, Y_3, Y_4, Y_5, Y_6 each represents H; one of Q_1 and Q_2 represents H; Y_7 and Y_8 each represents an optionally substituted aryl group, wherein the substituents are selected among alkyl and haloalkyl; Y_9 represents tri-alkyl silyl.

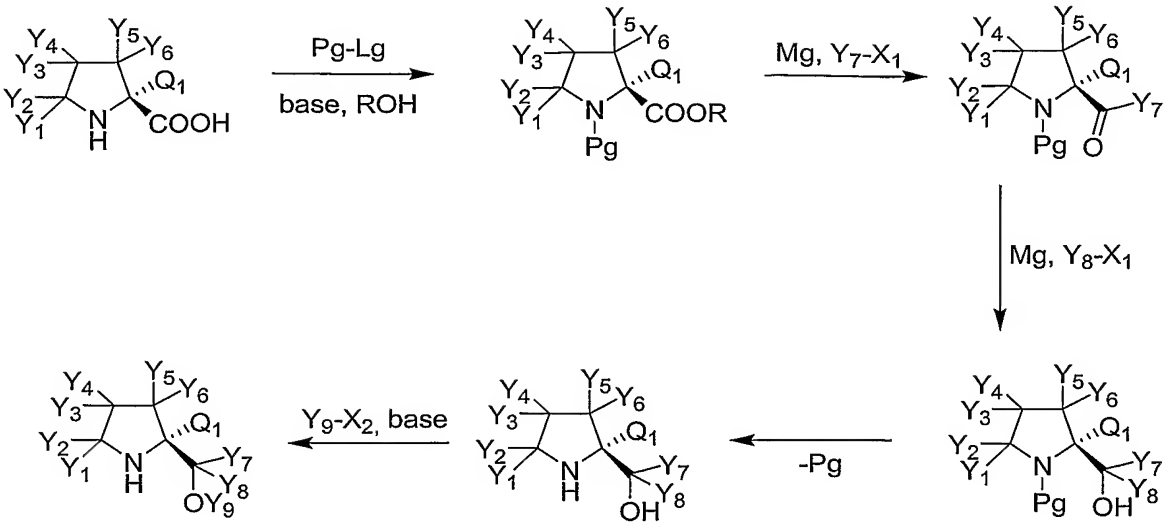
In an even more preferred embodiment Y_1, Y_2, Y_3, Y_4, Y_5, Y_6 each represents H; Y_7 and Y_8 each represents 3,5-di-trifluoromethyl phenyl and Y_9 represents trimethyl silyl.

Illustrative examples of compounds of the formula (4) are shown in Table 1b

Table 1b

Structure	Name
	(*S*)-2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine
	(*S*)-2-[bis-(3,5-dimethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine
	(*S*)-2-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidine
	(*S*)-2-[(*tert*-butyl-dimethyl-silanyloxy)-diphenyl-methyl]-pyrrolidine
	(*S*)-2-(di-naphthalen-1-yl-trimethylsilanyloxy-methyl)-pyrrolidine

The compounds of formula (4) are prepared according to the following reaction scheme:



where Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Q_1 are as previously defined; Pg represents a protecting group such as C(O)O-alkyl; Lg a leaving group such as chloride; X_1 represents *e.g.* chloro, bromo or iodo and X_2 represents *e.g.* a halogen or triflate.

The invention is illustrated by the following non-limiting examples:

Example 1 – preparation of (*R*)–2-chloro-3-methylbutanal

0.57 g (5.0 mmol) of (L)-prolinamide is added to a stirred solution of 5.4 ml (50 mmol) of 3-methylbutanal in 65 ml of CH_2Cl_2 cooled to 0 °C in an ice bath. 8.7 g (65 mmol) of N-chlorosuccinimide is then added, the ice bath removed and the mixture allowed to warm to 20 °C. Stirring is continued until the aldehyde is consumed as shown by ^{1}H-NMR and gas chromatography (GC) of the mixture after 1-2 h. 200 ml of pentane is then added, and the precipitated solids filtered off. The solvent is then evaporated, and 50 ml of pentane added to the residue. After filtration and evaporation of the pentane (*R*)-2-chloro-3-methylbutanal was obtained. Yield 5.1 g (85% of theory). The compound is identical to an authentic racemic sample on non-chiral GC and ^{1}H-NMR. The ee is determined to be 80% by GC on a Chrompack CP-Chirasil Dex CB-column, and the absolute configuration determined as (*R*) by reduction to 2-chloro-3-methyl-butan-1-ol with $NaBH_4$ in MeOH and comparison of the optical rotation of this product with the literature value (Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, page 317).

Example 2

Using the procedure as in Example 1, the following 2-chlorocarbonyls were obtained:

Table 2

Compounds of the formula (1a) or (1b) wherein X is Cl.

R	R_2	R_1	Catalyst	Yield (%)	Ee (%)
Ethyl	H	H	L-prolinamide	99	80(*R*)
Methyl	H	H	- " -	99	75(*R*)
Iso-Propyl	- " -	- " -	- " -	>90	87(*R*)
n-Hexyl	- " -	- " -	- " -	95	70(*R*)
Allyl	- " -	- " -	- " -	>90	74(nd)
Benzyl	- " -	- " -	- " -	75	78(nd)
Phenyl	H	CH_3	- " -	20	16(nd)
$-(CH_2)_4-$		H	- " -	30	76(nd)
Ethyl	H	H	(2*R*,5*R*)-diphenyl pyrrolidine	>90	95(*S*)
Methyl	- " -	- " -	- " -	99	31(nd)
Iso-Propyl	- " -	- " -	- " -	>90	94(*S*)
tert-Butyl	- " -	- " -	- " -	30	95(nd)
n-Hexyl	- " -	- " -	- " -	99	95(*S*)
Allyl	- " -	- " -	- " -	>90	95(nd)
Benzyl	- " -	- " -	- " -	82	95(nd)

nd = absolute configuration not determined

Example 3 – preparation of (*R*)-2-chloro-3,3-dimethylbutanal

5.7 mg (0.05 mmol) of (L)-prolinamide is added to a stirred solution of 50 mg (0.5 mmol) of 3,3-dimethylbutanal in 1 ml of CH_2Cl_2 cooled to -78 °C in a dry ice bath. 87 mg (0.65 mmol) of *N*-chlorosuccinimide is then added, and the mixture is warmed to -24 °C. Stirring is continued at –24 °C until the aldehyde is consumed as shown by ^{1}H-NMR and GC of the mixture (approx. 12 h). The yield of (*R*)-2-chloro-3,3-dimethylbutanal is determined by GC to

be >90% of theory. The ee is determined to be 95% by GC on a Chrompack CP-Chirasil Dex CB-column, and the absolute configuration determined as (*R*) by X-ray crystallography after reduction to (2*R*)-chloro-3,3-dimethylbutan-1-ol with $NaBH_4$.

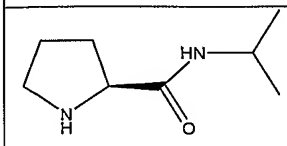
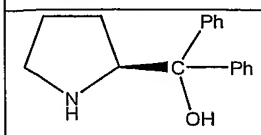
Example 4 – preparation of 2-chloro-4-(*tert*-butyldimethylsilyloxy)-butanal

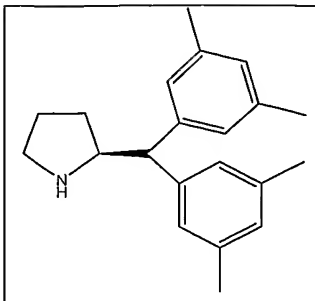
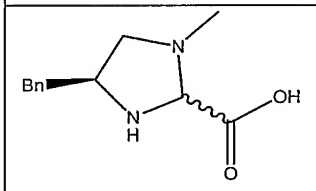
By the procedure in Example 3, employing 0.10 ml (0.50 mmol) of 4-(*tert*-butyldimethylsilyloxy)-butanal, (2*R*)-chloro-4-(*tert*-butyldimethylsilyloxy)-butanal was obtained. Yield 95% of theory, 81% ee, absolute configuration not determined.

Example 5 - preparation of enantiomers of 2-chloro-3-methylbutanal

Using the procedure as in Example 1 with 3-methylbutanal, the following results using various catalysts and 1.3 equivalents of *N*-chlorosuccinimide were obtained:

Table 3

Catalyst	Catalyst mol%	Reaction time (h)	Solvent	Yield (%)	Ee (%)
L-proline	20	1	$CHCl_3$	>95	23(*R*)
- " -	20	1	CH_2Cl_2	>95	25(*R*)
2-methyl-L-proline	20	5	DCE	76	60(*R*)
L-prolineamide	20	3	DCE	>95	78(*R*)
- " -	20	1	EtOH	<5	28(*R*)
- " -	20	1	THF	23	30(*R*)
- " -	10	1	CH_2Cl_2	>95	82(*R*)
	20	0.5	DCE	>95	54(*R*)
L-prolylglycine	20	1	DCE	33	81(R)
L-prolinol	20	1	DCE	34	77(*R*)
	20	1	DCE	15	85(*R*)

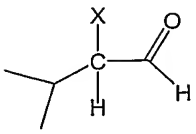
	20	0.5	DCE	92	64(*S*)
(2*R*,5*R*)-diphenylpyrrolidine	20	0.5	DCE	>95	94(*S*)
- " -	10	1	DCE	>95	94(*S*)
- " -	5	1	DCE	77	94(*S*)
(2*R*,5*R*)-dibenzylpyrrolidine	20	1	DCE	<10	78(*R*)
L-prolyl-L-leucine	20	1	DCE	39	57(*R*)
L-prolyl-L-phenylalanine	20	1	DCE	31	59(*R*)
L-prolyl-L-alanine	20	1	DCE	21	61(*R*)
	20	1	DCE	52	23(*S*)
(1*R*,2*R*)-cyclohexanediamine	10	18	CH_2Cl_2	18	15(*R*)
(1*R*,2*R*)-diphenylethanediamine	10	18	CH_2Cl_2	16	73(*R*)

DCE = 1,2-Dichloroethane, THF = Tetrahydrofuran.

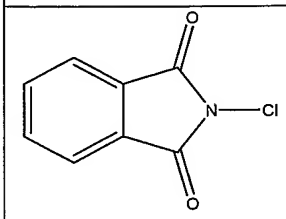
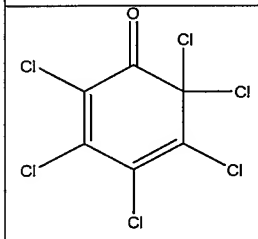
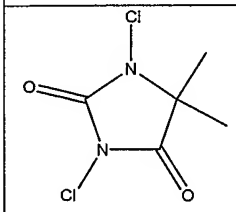
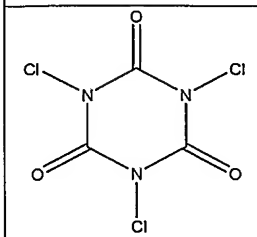
Example 6

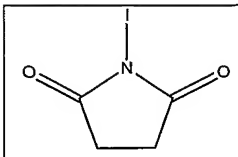
Using the procedure as in Example 1 with 3-methyl butanal, the following results using different halogenating reagents and 20 mol% of various catalysts:

Table 4



(1')

Halogenation agent	Equivalents relative to compound (2)	Catalyst	Solvent	Yield (%)	Ee (%)
 X=Cl	2.0	L-prolinamide	DCE	17	76(*R*)
- " -	2.0	(2*R*,5*R*)-diphenylpyrrolidine	DCE	26	93(*S*)
 X=Cl	1.3	(2*R*,5*R*)-diphenylpyrrolidine	CH_2Cl_2	80	95(S)
 X=Cl	1.3	(2*R*,5*R*)-diphenylpyrrolidine	CH_2Cl_2	12	76(*S*)
 X=Cl	1.0	L-prolinamide	CH_2Cl_2	20	61(R)

 X=I	2.0	(2*R*,5*R*)-diphenylpyrrolidine	DCE	100	24(nd)
- " -	2.0	L-prolinamide	DCE	22	13(nd)

DCE = 1,2-Dichloroethane.

nd = absolute configuration not determined.

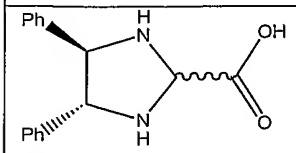
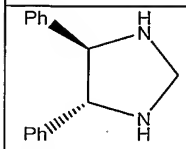
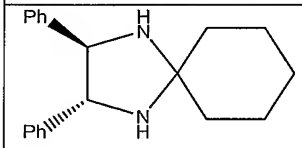
Example 7 – preparation of 2-bromo-3,3-dimethylbutanal

11.1 mg (0.05 mmol) of (2*R*,5*R*)-diphenylpyrrolidine is added to a stirred solution of 50 mg (0.5 mmol) of 3,3-dimethylbutanal in 1 ml of CH_2Cl_2 cooled to -78 °C in a dry ice bath. 115.7 mg (0.65 mmol) of *N*-bromosuccinimide is then added, and the mixture is warmed to -24 °C. Stirring is continued at -24°C until the aldehyde is consumed as shown by ^{1}H-NMR and GC of the mixture (approx. 2 h). The yield of 2-bromo-3,3-dimethylbutanal is determined by GC to be ca. 10% of theory. The ee is determined to be 80% by GC on a Chrompack CP-Chirasil Dex CB-column, absolute configuration not determined.

Example 8 – preparation of 2-chlorocyclohexanone

A series of experiments were performed to prepare optically active 2-chlorocyclohexanone from cyclohexanone in the presence of various catalysts using the following procedure: To a mixture of cyclohexanone and catalyst in CH_2Cl_2 was added *N*-chlorosuccinimide (0.5 mmol) and the reaction mixture stirred at ambient temperature for the time indicated in Table 5. Ee was determined by CSP-GC and the yield determined by GC.

Table 5

Catalyst	Cyclohexanone (mmol)	Catalyst mol%	Reaction time (h)	Yield (%)	Ee (%)
L-prolinamide	2.5	20	24*	40	81(R)
L-methyl prolinate	2.5	20	24	20	20(R)
	2.5	20	0.75	10	62(R)
	2.5	20	20**	88	95(R)
	2.5	20	22	17	88(R)

* Reaction performed at -24 °C. ** Reaction performed at -10 °C.

Example 9 – influence of addition of organic acids

A series of experiments were performed to prepare optically active 3-chlorotetrahydropyran-4-one from tetrahydropyran-4-one, in various solvents using (*R*,*R*)-4,5-diphenylimidazolidine as catalyst and in the presence of an organic acid, by the following procedure: To a mixture of tetrahydropyran-4-one, organic acid (0.4 molar equivalent), solvent (1 mL), and the catalyst (0.05 mmol), was added *N*-chlorosuccinimide and the reaction mixture stirred at -10 °C for a period of 24 h. Ee was determined by CSP-GC and the yield determined by GC.

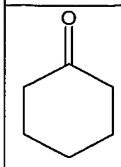
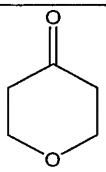
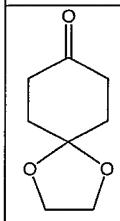
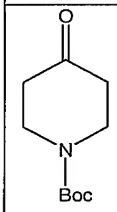
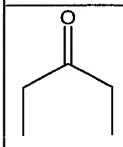
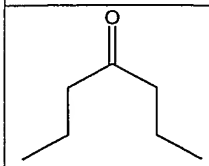
Table 6

Tetrahydro-pyran-4-one (mmol)	Acid	Solvent	NCS (Equiv.)	Yield (%)	Ee (%)
5	-	CH_2Cl_2	1	30	30
5	$PhCO_2H$	CH_2Cl_2	1	53	84
2.5	$PhCO_2H$	MeCN	1	15	97
2.5	AcOH	MeCN	1	19	87
5	CF_3CO_2H	CH_2Cl_2	1	62	68
2.5	$ClCH_2CO_2H$	MeCN	1	50	91
1	2-NO_2-$PhCO_2H$	MeCN	1.5	63	97
1	2-NO_2-$PhCO_2H$	MeCN	2.0	72	98

Example 10 – preparation of α-halo cyclic and acyclic ketones

A series of experiments were performed to prepare optically active α-halo cyclic and acyclic ketones from the corresponding ketone using the following general procedure: To mixture of ketone, (*R*,*R*)-4,5-diphenylimidazolidine as catalyst and 2-NO_2-$PhCO_2H$ in MeCN was added *N*-chlorosuccinimide (1.0 mmol) and the reaction stirred for a period of 20 h. Ee was determined by CSP-GC and the yield determined by ^1H NMR using an internal standard and confirmed using GC analysis.

Table 7

Ketone (mmol)	2-NO_2-$PhCO_2H$ (mmol)	Catalyst (mmol)	Reaction temp (°C)	Yield (%)	Ee (%)
 (0.5)	0.25	0.1	-24	82	97
 (0.5)	0.125	0.05	-24	72	98
 (0.5)	0.25	0.1	-24	83	90
 (0.5)	0.25	0.1	-24	76	93
 (2.5)	0.25	0.1	-10	62	83
 (2.5)	0.25	0.1	-10	40	88

Example 11 – preparation of α-bromo cyclohexanone

A series of experiments were performed to prepare α-bromo cyclohexanone:

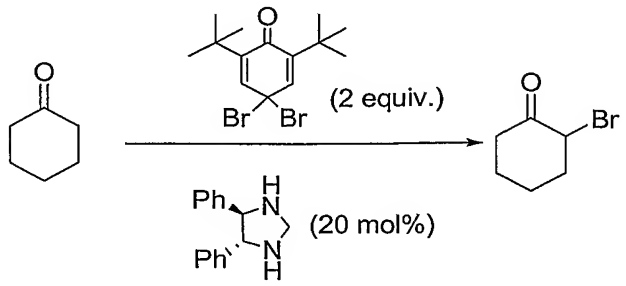


Table 8

Acid (mol%)	Temp (°C)	Solvent	Time (h)	Yield (%)	Ee (%)
2-NO_2-PhCO_2H (40)	-10	MeCN	3.5	30	83
2-NO_2-PhCO_2H (40)	-24	MeCN	20	32	82
2-NO_2-PhCO_2H (40)	-10	Et_2O	20	86	80
2-NO_2-PhCO_2H (40)	-10	Et_2O	2.5	65	88
None	-10	CH_2Cl_2	1	5	>99
2-NO_2-PhCO_2H (40)	-10	Toluene	3	25	90
2-NO_2-PhCO_2H (40)	-10	Toluene	20	60	82
2-NO_2-PhCO_2H (40)	-10	Acetone	5	57	88
AcOH (40)	-10	CH_2Cl_2	2	47	89
AcOH (40)	-10	CH_2Cl_2	20	52	86
PhCO_2H (40)	-10	CH_2Cl_2	20	79	83
PhCO_2H (40)	-24	CH_2Cl_2	4.5	65	86
PhCO_2H (40)	-24	Et_2O	20	60	89

Example 12 – preparation of α-bromo tetrahydropyran-4-one

A series of experiments were performed to prepare α-bromo tetrahydropyran-4-one:

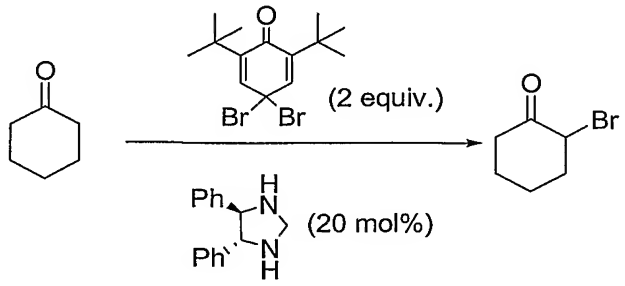
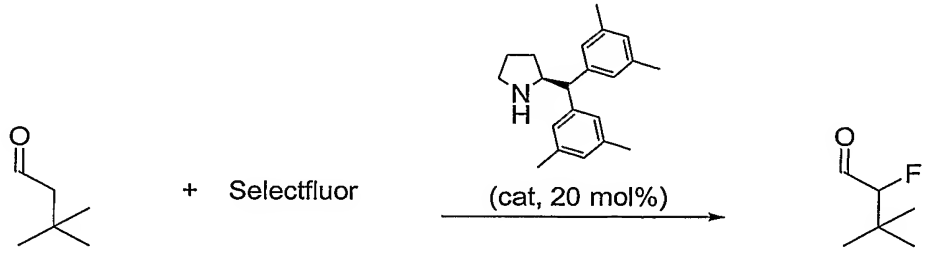


Table 9

Acid (mol%)	Temp (°C)	Solvent	Time (h)	Yield (%)	Ee (%)
$PhCO_2H$ (40)	-30	THF	20	66	88
$PhCO_2H$ (40)	-30	THF	40	82	85
$PhCO_2H$ (40)	-30	t-$BuOCH_3$	40	61	86
$PhCO_2H$ (40)	-30	THF	40	97	89

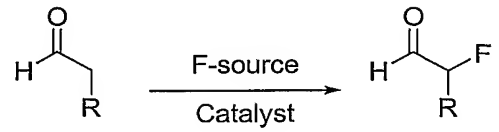
Example 13 – preparation of α-fluoro-3,3-dimethylbutanal



The catalyst (0.1 mmol) and 3,3-dimethyl-butyraldehyde (0.5 mmol) are stirred in CH_3CN (1.0 mL) for 30 min at room temperature. Selectfluor (106 mg, 0.60 mmol, 1.2 eq.) is added and the reaction mixture is stirred for 20 h. GC analysis showes 65% conversion of the aldehyde and 71% ee for the α-fluoro-3,3-dimethylbutanal. Selectfluor is a trademark of Air Products, and the compound name is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Example 14 – preparation of α-fluoro aldehydes

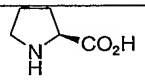
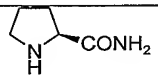
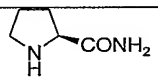
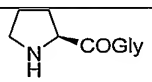
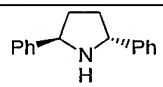
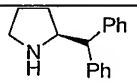
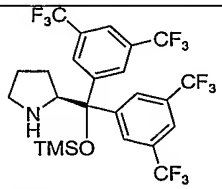
A series of experiments were performed using different aldehydes, fluorinating agents and catalysts at room temperature:

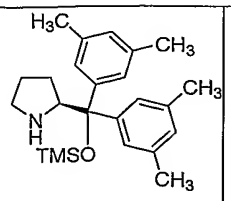
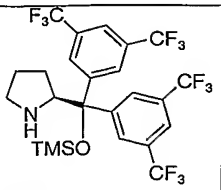
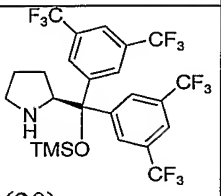
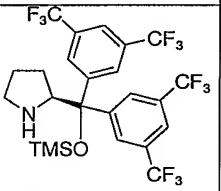
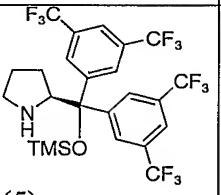
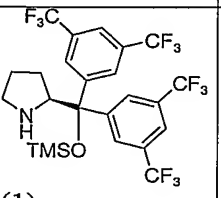
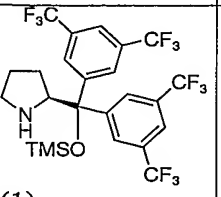


a: R = *t*-Bu
b: R = Bn

a: R = *t*-Bu
b: R = Bn

Table 10

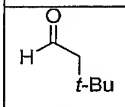
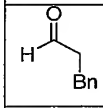
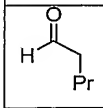
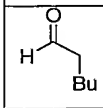
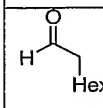
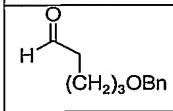
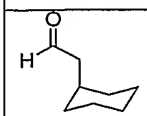
Aldehyde	Catalyst (mol%)	Fluor source	Solvent	Time (h)	Conversion (%)	Ee (%)
1a	 (20)	Selectfluor	MeCN	20	88	34
1a	 (20)	Selectfluor	MeCN	20	98	24
1a	 (20)	NFSI	MeCN	1	38	27
1a	 (20)	Selectfluor	MeCN	20	98	45
1a	 (20)	Selectfluor	MeCN	1	24	78
1a	 (20)	Selectfluor	MeCN	20	63	71
1a	 (20)	NFSI	MeCN	20	90	94

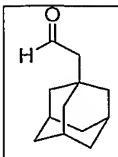
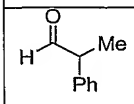
1a	 (20)	NFSI	MeCN	20	36	95
1b	 (20)	NFSI	MeCN	20	45	95
1b	 (20)	NFSI	CH_2Cl_2	20	58	97
1b	 (20)	NFSI	MTBE	1	96	93
1b	 (5)	NFSI	MTBE	1	77	96
1b	 (1)	NFSI	MTBE	2	92	93
1a	 (1)	NFSI	MTBE	2	>95	97

Example 15 – Procedure for the organocatalytic α-fluorination of aldehydes using NFSI as the fluorinating agent catalyzed by ((*S*)-2-[bis-(3-5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine.

The catalyst ((*S*)-2-[bis-(3-5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine, 0.005 mmol, 1 mol%) and the aldehyde (0.75 mmol, 1.5 eq.) are stirred in MTBE (1.0 ml) for 30 min at room temperature. NFSI (158 mg, 0.50 mmol, 1.0 eq.) is added and the reaction mixture is stirred for 2 h at room temperature. Conversion is determined by GC analysis. The yields are also confirmed after reduction of the catalytic product to the corresponding alcohol by the following procedure: Pentane (4.0 ml) is added and the precipitates are removed by filtration. MeOH (4.0 ml) is added followed by $NaBH_4$ (2 eq). The reaction is quenched after 1 h with a 1M solution of $KHSO_4$ and the product is extracted with Et_2O. The organic phase is dried on Na_2SO_4, filtrated and after evaporation of the solvent the alcohol is isolated by flash chromatography on silica.

Table 11

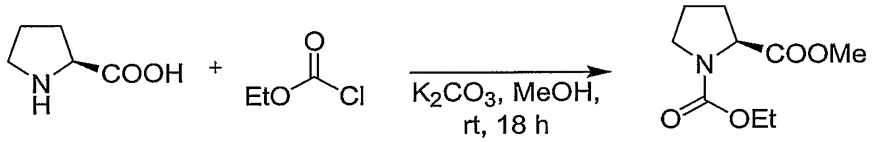
Aldehyde	Yield (%)	Ee (%)
	>90	97
	74	93
	74	96
	74	96
	55	96
	64	91
	60	96

	75	96
	70	53

Example 16 – preparation of the catalyst *(S)*-2-[bis-(3-5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine.

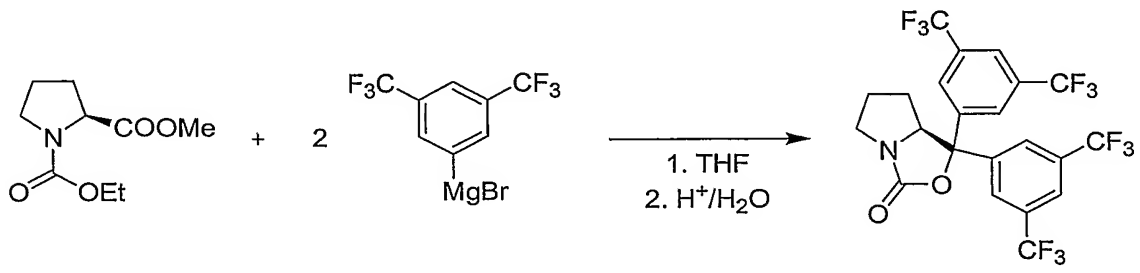
The catalyst ((*S*)-2-[bis-(3-5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine is prepared by a four steps synthesis from L-proline. The detailed procedures are the following:

1. Preparation of *(S)*-pyrrolidine-1,2-dicarboxyclic acid 1-ethyl ester 2-methyl ester:



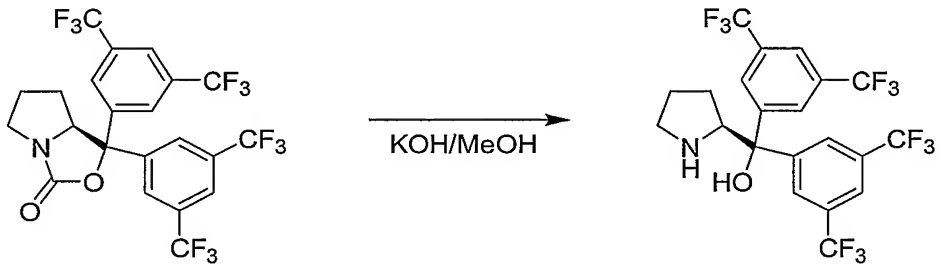
45 ml (477 mmol) of ethyl chloroformate is added to a stirred suspension of 25 g (217 mmol) L-proline and 30 g (217 mmol) potassium carbonate in 300 ml MeOH. The reaction is stirred at ambient temperature overnight. Evaporation of the solvent, addition of 200 ml water, extraction with CH_2Cl_2 (4 x 100 ml), drying of the organic phase over Na_2SO_4 and removal of the solvent yield 44 g (99%) of the pure product.

2. Preparation of *(S)*-1,2-bis-(3,5-bis-trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one:



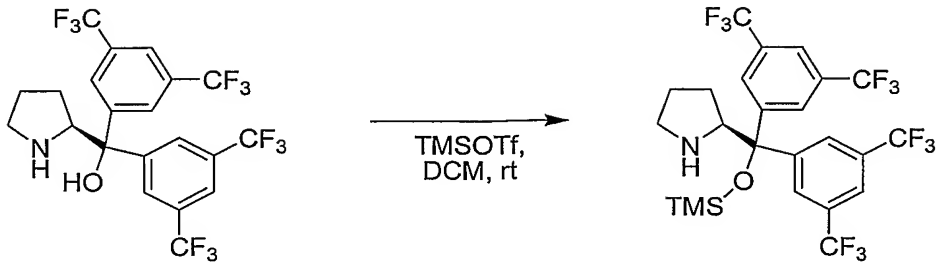
0.84 g (34 mmol) of Mg is suspended in 20 ml of dry THF under a N_2 atmosphere and a solution of 5.9 ml (34 mmol) of 2,5-bis(trifluoromethyl)bromobenzene in 60 ml of dry THF is added slowly. Afterwards the mixture is heated up to reflux for 1 h. The reaction is cooled down to 0 °C and a solution of 3.11 g (15 mmol) pyrrolidine-1,2-dicarboxyclic acid 1-ethyl ester 2-methyl ester in 50 ml of dry THF is added. Then the reaction is allowed to reach room temperature before refluxing for 2 h. The reaction mixture is cooled down to room temperature and then poured into a mixture of ice and saturated NH_4Cl solution. Extraction with EtOAc (3 x 50 ml), drying over Na_2SO_4 and evaporation of the solvent yield 49.0 g (99%) of a dark brown solid/oil. Recrystallisation from Et_2O yield 4.3 g (50%) of the product as a white solid.

3. Preparation of *(S)*-bis-(3,5-bis-trifluoromethyl-phenyl)-pyrrolidin-2-yl-methanol:



4.3 g (76 mmol) KOH and 4.2 g (7.6 mmol) *(S)*-1,2-bis-(3,5-bis-trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one are suspended in 20 ml MeOH and heated up to reflux for 2 h. After reaching ambient temperature and removal of the solvent water is added and the mixture is extracted with CH_2Cl_2. Drying over Na_2SO_4 and evaporation yield 4.2 g (99 %) of the product as a colorless oil.

4. Preparation of *(S)*-2-[bis-(3-5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine



2.0 ml (11.4 mmol) TMSOTf is added at 0 °C to a solution of 4.0 g (7.6 mmol) *(S)*-bis-(3,5-bis-trifluoromethyl-phenyl)-pyrrolidin-2-yl-methanol and 1.59 ml (11.4 mmol) Et_3N in 50 ml CH_2Cl_2. The reaction is then allowed to reach ambient temperature and stirred for 1 h until full conversion of the starting material is confirmed by TLC analysis. The reaction is quenched with water, the product extracted with CH_2Cl_2 (3 x 30 ml) and dried over Na_2SO_4. After evaporation of the solvent the product was purified by flash chromatography on silica (pentane:CH_2Cl_2 = 2:1) to yield 3.8 g (84%) of the catalyst as a yellow oil, which after precipitation affords a colorless solid.